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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/627,556	LEDBETTER ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58,61-79 and 81-110* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28,31-58,61-79,81,82,109 and 110* is/are rejected.

7)☒ Claim(s) *29, 30 and 83-108* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/07 has been entered.

2. Claims 1-58, 61-79 and 81-110 are all the pending claims for this application.

3. New Claim 110 was added in the Response of 10/31/07.

4. Claims 1-58, 61-79 and 81-110 are all the pending claims under examination.

Withdrawal of Rejections

Claims - 35 USC § 112, first paragraph

Biological Deposit Requirement

5. The rejection of Claims 29, 30 and 83-108 under 35 U.S.C. § 112, first paragraph, because the specification does not indicate that biological deposits have been made for the hybridoma cell lines HD37 scFv, G28-1 scFv, 4.4.220 scFv, Fc2-2 scFv, UCHL-1 scFv, 5B9 scFv, L6 scFV, 10A8 scFV, 2e12 scFV, 40.2.36 scFV or G19-4 scFv is withdrawn.

Applicants' allegations on pp. 14-15 of the Response of 10/31/07 have been considered but are found persuasive. Applicants state that because the specification

has described the sequences for the variable regions from the antibodies of the hybridomas and they are publicly available, one skilled in the art could make and use the fusion proteins as claimed and the deposit of the hybridomas is not necessary.

Enablement

6. The rejection of Claims 29, 30 and 83-108 under 35 U.S.C. 112, first paragraph, in lacking enablement for the hybridoma cell lines, 2H7 scFv, HD37 scFv, G28-1 scFv, 4.4.220 scFv, Fc2-2 scFv, UCHL-1 scFv, 5B9 scFV, L6 scFv, 10A8 scFv, 2e12 scfV, 40.2.36 scFv, 1D8 scfV or G19-4 scFv, is withdrawn for the reasons set forth under section 5.

Rejections Maintained

Claims - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. The rejection of Claim 13 for the recitation "where leucine is replaced by des-leucine at position 11" is maintained.

Applicants' allegations on p. 14 of the Response have been considered but are not persuasive. Applicants state "the designation "des" preceding the name of the amino acid indicates that that particular amino acid has been deleted and no amino acid has

been substituted in its place" citing the JBC article (242:555-557 (1967)) on p. 555, Col. 1.

The examiner submits that the JBC article defines "des" on p. ***556***, Col. 1 as:

> "the compound obtained by the formal removal of an amino acid residue in position q from a polypeptide X is designated by the name des-q-aminoacid-X, abbreviated des-Abcq-X. Example: Des-7-Proline-oxytoxin; des-Pro7-oxytoxin."

Thus based on the art-recognized definition, it is not apparent how the leucine at position 11 can be *replaced* with a des-leucine as according to the instant claim. In fact, the meaning of the claim is contrary to the definition for a des residue which implies its removal. "Des-leucine" is not an amino acid residue *per se* as Applicants have been urging the Office to believe.

Claims - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement

8. The rejection of Claims 1-28, 31-58, 61-79, 81, 82 and 109 under 35 U.S.C. 112, first paragraph, in lacking enablement for a single chain antibody having antigen binding specificity for *any* antigen or a scFv having antigen binding specificity for *any* antigen and where the single chain antibody or scFv comprise *any* amino acid substitution or deletion in any one or more positions 9, 10, 11, 12, 108, 110 and 112 for the VH region

and *any* amino acid substitution or deletion in one or more of positions 12, 80, 81, 83, 105, 106 and 107 for the VL region is maintained.

Applicants' allegations on pp. 15-18 have been considered but are not found persuasive.

a) Applicants allege because the specification teaches: several references showing methods for engineering framework and CDR residues at [346], WO92/01787 and WO98/02462 which are incorporated by reference and describe residues of V domains in which substitutions can be made, Examples 20, 34, 35, 38, 41 and 42 demonstrate inventive scFv constructs, and methods for measuring functional properties of antibodies, the instant claims are fully enabled.

The examiner respectfully submits that the scope of all possible substitutions, deletions or combinations thereof for the designated residues of the VH and VL domains in the broadest claims could not be predicted by one of skill in the art to produce a mono- or bi-valent scFv with a) the same binding specificity as the parent antibody, b) have increased expression or stability over the parent antibody and c) be capable of at least one immunological activity.

Prior Art Status: CDR and framework interactions influence antigen recognition

At the time of Applicant's filing, the field of art acknowledged that amino acid composition influenced the conformation of CDR and framework interactions in variable domains which influenced binding and antigen recognition. Thus one could not

predictably mutate an amino acid residue in an immunoglobulin variable domain and expect that the properties of antigen binding and recognition would not be affected.

McCalllum *et al.* (J. Mol. Biol. (1996) 262:732-745), analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.).

Pascalis *et al.* (The Journal of Immunology (2002) 169, 3076-3084) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left col.).

Casset *et al.* (2003) BBRC 307, 198-205 constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset *et al.* also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and a framework residue located just before the H3 (see page 202, left col.).

Vajdos *et al.* (2002) J. Mol. Biol. 320, 415-428, additionally state that antigen binding is primarily mediated by the CDRs, and more highly conserved framework segments which connect the CDRs, are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.).

Holm *et al* (2007) Mol. Immunol. 44: 1075-1084 describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract).

Chen *et al.* J. Mol. Bio. (1999) 293, 865-881 describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866).

Wu *et al.* J. Mol. Biol. (1999) 294, 151-162 state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

Thus, while one can make the statement that the antibody or scFv can tolerate a limited number of changes at defined positions, the prior art recognizes that residues in both the CDRs and frameworks are shown to influence binding. In fact, the prior art as well as Applicants own disclosure do not support that it was clearly established, that

CDR domains alone are sufficient to define the binding specificity of an antibody or scFv, and that multiple antibodies or scFv can predictably be generated having the same binding specificity based on predetermined residues in addition to having increased expression or stability and immunological activity.

Analyzing applicants own disclosure, which while it does have scFvs with divergent variable domains, the data seem to indicate that it is the frameworks and CDRs that contribute to antigen binding, increased expression and stability.

Prior Art Status: Conservative Amino Acid Substitutions within CDR/FR Residues

The claims encompass polypeptides comprising VH domains and VL domains comprising conservative amino acid substitutions. It is not well established in the art that all variable domains are amenable to conservative modifications. Numerous publications acknowledge that conservative substitutions would in fact change the binding ability of antibodies if not substantially reduce the affinity.

Brummell *et al.* (Biochemistry 32:1180-1187 (1993)) found that mutagenesis of the four HCDR3 contact residues for the carbohydrate antibody (Salmomella B O-polysaccharide) in no instance improved affinity but 60% of the mutants resulted in a 10-fold drop in binding constant (affinity electrophoresis value of 0.85), while still other mutants were lower (Table 1 and p. 1183, Col. 2, ¶2 to p. 1184, Col. 1, ¶1). Brummell demonstrates that no substitution retained antigen binding affinity similar to the wild type antibody despite targeted, conservative substitutions in known contact sites.

Kobayashi *et al.* (Protein Engineering 12:879-844 (1999)) discloses that a scFv for binding a DNA oligomer containing a (6-4) photoproduct with Phe or Tyr substitutions at Trp 33 retained "a large fraction of the wild-type binding affinity, while the Ala substitution diminished antigen binding" (Table 1). However, Kobayashi notes "replacing Trp 33 with Phe or Ala alters the local environment of the (6-4) photodimer since binding is accompanied by large fluorescence increases that are not seen with the wild-type scFv" (p. 883, Col. 2, ¶3).

Burks *et al.* (PNAS 94:412-417 (1997)) discloses scanning saturation mutagenesis of the anti-digoxin scFv (26-10) which also binds digitoxin and digoxigenin with high affinity and with 42-fold lower affinity to ouabain. 114 mutant scFvs were characterized for their affinities for digoxin, digitonin, digoxignenin and oubain. Histogram analysis of the mutants (Figure 2) reveals that "not all residues are optimized in even high affinity antibodies such as 26-10, and that the absence of close contact with the hapten confers higher plasticity, i.e., the ability to tolerate a wider range of substitutions without compromising binding (p. 415, Col. 2, ¶4- p. 416, ¶1).

Although Brummell *et al.*, Kobayashi *et al.* and Burks *et al.* introduced conservative amino acid substitutions into CDRs to examine binding effects these three references do not overcome the unpredictability in the art as far as demonstrating that any conservative substitution within any CDR can be made without affecting binding.

Jang *et al.* (Molec. Immunol. 35:1207-1217 (1998)) teach that single amino acid mutations to the CDRH3 of a scFV derived from 2C10, an anti-dsDNA autoantibody, reduced the binding activity about 20-50% compared to the unmutated scFv (Table 4).

Brorson *et al.* (J. Immunol. 163:6694-6701 (1999)) teach that single amino acid substitutions to the CDRs of IgM Abs for the bacterial protein, levan, are ablated.

Coleman (Research in Immunol. 145:33-36 (1994)) teaches that single amino acid changes within the interface of an antibody-antigen complex are important and that inasmuch as the interaction can tolerate amino acid sequence substitutions, "a very conservative substitution may abolish binding" while "in another, a non-conservative substitution may have very little effect on the binding" (p. 35, Col. 1, ¶1).

The specification provides insufficient guidance regarding how to produce the genus of antibodies or scFvs as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

b) Applicants further allege the claims specify the amino acid positions which are to be changed and as such there are a limited number of choices to which a single amino acid can be altered, and because the residues in an immunoglobulin variable domain are highly conserved, one of skill in the art can readily determine which residues may be altered without undue experimentation.

Despite Applicants urging the Office that claimed scFv constructs would not be unlimited in number, one must consider that for the broadest claims, a given amino acid position can be substituted with any one of the known 23 amino acids. The broadest claims are not limited to preferred amino acid substitutions. The broadest claims encompass scFvs comprising amino acid substitutions occurring in any one or more positions 9, 10, 11, 12, 108, 110 and 112 for the VH region and in any one or more of

positions 12, 80, 81, 83, 105, 106 and 107 for the VL region thus a large number of possible combinations can be generated for the scFvs falling within scope of the claims.

Because the specification does not provide sufficient guidance for producing the myriad scFv constructs and the prior art recognizes the importance of amino acid interactions between the CDR and frameworks within variable regions for proper protein folding and antigen binding, the rejection of the claims for lack of enablement is maintained, and further where additional requirement of the invention is that the substitution, deletion or combination thereof confers increased expression and stability of the scFv.

Claims - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The rejection of Claims 1-12, 14-23, 25-28, 31-47, 52-55, 57, 58, 61-63, 65, 68, 69, 71, 72, 76-79 and 109 under 35 U.S.C. 103(a) as being unpatentable over Shan et al (J. Immunol. 162:6589-6595 (1999); hereinafter referred to as "Shan"; cited in the IDS of 7/2/04) in view of Pluckthun et al. (USPN 6,815,540; published 11/9/2004; filed 1/15/1999; hereinafter referred to as "Pluckthun") is maintained.

Applicants' allegations on pp. 19-21 of the Response of 10/31/07 have been considered but are not persuasive.

Applicants allege Shan teaches monovalent constructs are not as useful as bivalent constructs and that Shan does not teach any construct (mono- or bi-valent) having a change in the VH domain at position 11. Pluckthun teaches that changes at position 11 to asparagine show nearly no effect on increased solubility while aspartic acid shows some effect while changes at residues 84, 87 and/or 89 imparts dramatically improved solubility properties. Further, that a leucine substitution at position 11 in the scFv of Example 34 in Applicant's specification shows improved expression levels and is unexpected.

The examiner respectfully submits that both Shan and Pluckthun appreciate the advantages of producing smaller antibody fragments in order to reduce immunogenicity and allow for greater penetration into targeted sites. Applicants own dependent claims 4 and 5 are drawn to bivalent antibodies so Claim 1 would encompass mono- and bivalent antibodies. Improvements to bivalent antibodies and monovalent antibodies were taught by Shan in combination with Pluckthun. The motivation to produce a small sized scFv antibody having improved expression or stability would have been provided by Pluckthun. Pluckthun may suggest that substitution of position 11 was not as effective as substituting other positions, but Pluckthun's effect at position 11 was observable. As restated from the previous Office Action:

> "The instant generic claims are not limited by any amount to which the increased expression or stability of the protein must be achieved for the substitution or deletion of position 11 in the VH domain relative to the

parent antibody, and yet still retain antigen binding and possess at least one immunological activity."

Applicants' argument that Pluckthun provides no motivation to substitute position 11 because the results in Pluckthun's hands were "not very dramatic" is dispositive to the fact that the claims are not even limited to a quantifiable or quantified amount of an improvement. Any improved expression or stability by a substitution at position 11 would read on the instant claims. Applicants' argument that the claims are distinguishable over Shan and Pluckthun because the substitution at position 11 is unexpected is implausible because Pluckthun shows a measurable, quantifiable change in the output of the scFv at the same position. *Pluckthun discloses an example of a scFv mutant at VH position 11 (Flu6 (L11D/V84D) (FIG. 3B lane 7, 8)) that yielded about 0.25 mg per liter of protein whereas the wt scFv antibody did not give any soluble protein.* Applicants should reconcile the specific data in Pluckthun and the general disclosures of Pluckthun and Shan for producing improved mono- and bi-valent scFvs with the breadth of their own claim scope. The rejection is maintained.

10. The rejection of Claims 1, 56, 65 and 70-72 under 35 U.S.C. 103(a) as being unpatentable over Shan in view of Pluckthun as applied to claim 1 above, and further in view of Bodmer et al. (USPN 5,677,425; published 10/14/1997; hereinafter referred to as "Bodmer"; cited in the IDS of 12/22/04) is maintained.

Applicants' allegations on pp. 21-22 of the Response have been considered but are not persuasive. Applicants allege that Shan and Pluckthun do not provide motivation

to produce a scFv with a modification at position 11 of the VH and that Bodmer does not rectify this deficiency.

The examiner's discussion regarding Shan and Pluckthun is set forth supra, and where each reference discloses modifications for scFvs, and where Pluckthun specifically discloses increased yield by the specific substitution at position 11 of VH, one skilled in the art could readily have further modified the construct of Shan in view of Pluckthun and Bodmer, because Bodmer teaches constant regions, cysteine-altered hinges and humanized antibodies, which would not effect the product yield of the scFvs of Shan and Plucktun.

11. The rejection of Claims 1, 63, 66 and 82 under 35 U.S.C. 103(a) as being unpatentable over Shan in view of Pluckthun as applied to claims 1 and 77 above, and further in view of Bodmer and Morrison et al. (USPN 6,284,536; published 9/4/2001; filed 8/11/98; hereinafter referred to as "Morrison"; cited in the IDS of 3/21/05) is maintained.

Applicants' allegations on pp. 22-23 of the Response have been considered but are not persuasive. Applicants allege that Shan, Pluckthun and Bodmer do not provide motivation to produce a scFv with a modification at position 11 of the VH and that Morrison does not rectify this deficiency.

The examiner's discussion regarding Shan, Pluckthun and Bodmer are set forth supra, and where each reference discloses modifications for scFvs, and Pluckthun specifically discloses increased yield by the specific substitution at position 11 of VH,

one skilled in the art could readily have further modified the construct of Shan in view of Pluckthun, Bodmer and Morrison, because Morrison teaches modified antibodies having IgA regions, which would not effect the product yield of the scFvs of Shan in view of Plucktun and Bodmer.

12. The rejection of Claims 1, 64, 67 and 73-75, 77 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shan in view of Pluckthun as applied to claims 1 and 77 above, and further in view of Roux et al. (J. Immunol. 161:4083-4090 (1998); hereinafter referred to as "Roux") is maintained.

Applicants' allegations on pp. 23-24 of the Response have been considered but are not persuasive. Applicants allege that Shan and Pluckthun do not provide motivation to produce a scFv with a modification at position 11 of the VH and that Roux does not rectify this deficiency.

The examiner's discussion regarding Shan and Pluckthun are set forth supra, and where each reference discloses modifications for scFvs, and Pluckthun specifically discloses increased yield by the specific substitution at position 11 of VH, one skilled in the art could readily have further modified the construct of Shan in view of Pluckthun and Roux, because Roux teaches modified antibodies having IgE and IgG1 hinge regions and praline-substituted cysteine residues in hinges, which would not effect the product yield of the scFvs of Shan in view of Pluckthun.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claim 110 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 110 is indefinite for the recitation "G28-2VHL11S (SSC-P) H WCH2WCH3 set out in SEQ ID NO: 329". What does "set out" mean with respect to the relationship between the protein, the construct and SEQ ID NO:329?

Conclusion

14. No claims are allowed.

15. Claims 29, 30 and 83-108 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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